DETAILED ACTION

Applicant's response dated 04/26/2011 is acknowledged and entered.

Election/Restrictions

Applicants' election of Group III (claims 17-26), drawn to a method of targeting a stem cell to a target tissue in a subject by *ex vivo* cell therapy is noted. Claims currently encompass non-elected embodiments and such subject matter should be removed from the claims prior to allowance.

Elected species are heart as a target tissue, viral vectors, MLC-2v as the tissue-specific promoter, and hSDF-1 as the stem cell-attracting chemokine.

Claims 17 and 34 are amended. Claims 1-16,19,25-28 and 30-31 are cancelled. Claim 47 is added.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-18,20-24,29,32-46 remain rejected and newly added claim 47 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant invention is drawn to a method to recruit stem cells, either endogenous or exogenously administered, to a site in the body where those stem cells are needed to replenish a healthy supply of differentiated cell types. The invention is drawn to carrying out such a method using a vector system with elements that result in expression of a stem cell-attracting chemokine in an area of need.

The claims encompass both in vivo and ex vivo gene therapy. However, Applicant has elected ex vivo gene therapy (i.e. cell therapy) for examination. The specification contemplates ex vivo gene therapy, or cell therapy, at page 16 of the specification, where it teaches introducing the vector system of the invention into stem cells followed by transplantation of the cells back into the host. The specification teaches that any of numerous administration routes can be used to deliver the cells, including jugular vein, tongue vein, IP and IV injection.

The specification provides a working example that teaches gene therapy, or direct injection of the plasmid vectors into the host. In example 2, the target tissue is the heart and the plasmids were delivered by intracardial injection, right to the site of need. The specification does not teach, by way of example, the elected invention of ex vivo gene therapy. The specification does not provide guidance regarding how cells carrying the plasmid constructs will reach the desired tissue location and does not teach what cell types can be used to deliver and express the plasmid constructs in each desired location. Thus, for example, the claims encompass IV injection of epithelial cells comprising the polynucleotides of the claims, with the goal of targeting stem cells to the heart. The specification does not support that any cell type will, itself, home to the desired location, and express the chemokine that is intended to attract stem cells to that location. After all, the object of the invention is to aid in the homing of cells to the tissue of interest.

It is noted that the claims are not limited to the elected invention or species. Applicant elected used on the MLC-2v promoter, which is active in heart cells, not any cell type encompassed by the claims. Thus, in light of the election of the MCL-2v promoter, claims should be limited to use of cell types in which the elected promoter would be active. Without such a limitation, the claims are not enabled because the nucleic acid construct of the invention will not be expressed in any cell type in which the MLC2v promoter is not active.

As set forth at pages 4-5 of the office action dated 10/26/2010, successful attempts at cell therapy in the heart are limited with regard to the cell types used as well as the delivery method. In general, cardiomyocytes or multipotent stem cells with the capacity to differentiate into cardiac cells are used and the cells are transplanted directly into the heart. Difficulties associated with use of stem cells include the inability to obtain an effective quantity of a desired stem cell type from an individual. Use of ES cells to overcome this difficulty poses problems of immune compatibility as well as undesired effects of the transplanted cells (see page 409).

Other unpredictable factors complicate cellular transplantation including problems of cell isolation and purification, cellular environment, the immune response to transplanted cells, as well as the preservation of cells used in cellular transplantation. Inverardi et al. discuss the genetic engineering of cells to be used in cellular transplantation, and discuss the limitations of currently available gene delivery systems (see p. 685). Additionally, transgene expression can abruptly cease in transplanted, recombinant cells, and it cannot be due to cell loss or gene deletion because the transplanted cells can be recovered. The specification fails to teach how to overcome the aforementioned unpredictabilities associated with the ex vivo gene therapy art.

Claim 17 has been amended to limit the target tissue. This, however, fails to address the issues associated with the breadth of the claims and unpredictabilities as outlined above and set forth in the office action dated 10/26/2010. The invention involves administering stem cells comprising a vector system that results in expression of a stem cell-attracting chemokine that will 'home' stem cells from other sites in the body to the target cardiac tissue. However, as set forth above, the claims encompass any mode of administration, administering the polynucleotides via any type of cell. The need for the invention, a signal to enrich or enhance migration of stem cells to a target, is the basis for the lack of enablement of the ex vivo gene therapy to provide a signal for targeting of other stem cells to the target tissue.

In light of claim 44, it appears Applicant may be intending for the chemokine to be expressed by stem cells that are the same cells as those to be targeted. Thus, it appears the cells express their own homing signal. If this is the case, then the cells are likely to stay wherever they are administered. Claim 17, however, encompasses use of any cell type to administer the claimed polynucleotides and then stem cells to be recruited to the site of polynucleotide wxpression can be endogenous, naturally existing stem cells, or stem cells that are administered exogenously.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 44 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 has been amended but remains unclear. Claim 17 already requires administration of a nucleic acid that encodes a cell-attracting chemokine. It is not clear if claim 44 is adding additional steps of administering an additional cell-attracting agent or if it is limiting the method steps already recited in claim 17. If cells are administered to the target, it is not clear what function an agent that causes migration to the target would have.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-18,20-22,24 and 32-36 remain rejected and newly added claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Petersen et al. (U.S. Patent Publication No.: 2002/0094327; effective filing date: Nov. 5, 2000), in view of Phillips et al. (Hypertension 39(part 2):651-655, 2002), and further in view of Tang et al. (Hypertension, 39(part 2):695-698, 2002). The rejection is maintained for reasons of record set forth at pages 3-6 of the office action dated 07/14/2009. Applicant's arguments have been fully considered and are not persuasive.

Applicant argues that the lack of teachings of the claimed invention in a single reference is evidence of the nonobviousness of the combination of the teachings. Applicant argues that there was no motivation to make to combination of references and there would not have been a reasonable expectation of success in making such a combination. Applicant asserts that arriving at the claimed invention required more than simple substitution of a chemokine gene for a therapeutic gene and that the claims are amended to now recite that the target tissue is damaged or at risk of damage and that the claimed method results in reduced damage or reduced risk of damage. Applicant argues that the references cited do not teach or suggest that damage to the target tissue could be reduced or repaired.

In response, Petersen, the primary reference, teaches expression of a chemokine to attract stem cells to a target. The only difference between Peterson and the claimed invention is the structure and

regulation of the vector system. The purpose of attracting stem cells to cardiac tissue is to repair tissue. The therapeutic genes of Phillips are not being substituted with a chemokine of Petersen. Rather, the method of Petersen is being modified to add vector control elements known in the art. There is no evidence of record that one of skill in the art could not modify the nucleic acid vectors of Petersen to appropriately utilize control systems of other known vectors.

The examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007).

Claims 17,23 and 44 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Petersen et al. (U.S. Patent Publication No.: 2002/0094327; effective filing date: Nov. 5, 2000), in view of Phillips et al. (Hypertension 39(part 2):651-655, 2002), and Tang et al. (Hypertension, 39(part 2):695-698, 2002), as applied to claims above, and further in view of Kovesdi (USPGPUB 2003/0027751). The rejection is maintained for reasons of record set forth at pages 6-7 of the office action dated 07/14/2009. Applicant's arguments have been fully considered and are not persuasive.

Applicant's arguments regarding this rejection were combined with those reiterated and addressed above. The rejection is maintained, therefore, for reasons set forth above.

Claims 17-18,20-22,24,29,32-43,45-46 remain rejected and newly added claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Petersen et al. (U.S. Patent Publication No.:

2002/0094327; effective filing date: Nov. 5, 2000), in view of Tang et al. (Methods, 28:259-266, 2002; referred to as Tang2).

The claims encompass a method of targeting a stem cell to the heart of a subject by *ex vivo* cell therapy, the method comprising administering to the heart tissue a composition comprising: (a) a first polynucleotide comprising: (1) a gene switch/biosensor comprising a nucleic acid sequence encoding a physiological stimulus-sensitive chimeric transactivator, and (2) an operatively linked MLC-2v cardiac promoter; and (b) a second polynucleotide comprising a nucleic acid sequence encoding the stem cell-attracting chemokine hSDF-1.

Petersen et al. describe a method of modulating the targeting of pluripotent stem cells to a target tissue of a mammalian subject by increasing the concentration of SDF-1 alpha protein in the target tissue (Abstract). The mammalian subjects include humans and non-humans (paragraph [0063], limitation of claim 17), and the target tissue can be the heart (paragraph [0063], p. 8, limitation of claim 19). Peterson states that the mammalian SDF-1 alpha genes, including the human gene are known (paragraph [0030], and may be used as part of a heterologous DNA under the control of a tissue-specific promoter (paragraph [0086]), using AAV-based vectors (paragraph [0084], limitation of claim 18). *Ex vivo* gene transfer of the SDF-1 alpha nucleic acid under the control of a tissue specific promoter to host cells , followed by delivery of the transfected cells to the host is described in paragraph [0104], p. 13 (limitation of claim 20). In Example 2, Petersen et al. describe SDF-1 alpha expression in a model of tissue injury (p. 14, limitation of claim 25). The authors additionally describe using agents that increase the transcription or translation of a gene encoding SDF-1 alpha in a target tissue, that may also be used in the invention (paragraph [0068], p. 9; limitation of claim 24), or using agonists (claim 1, p. 14), or G-CSF to increase the number of stem cells in the peripheral blood (paragraph [0009], p. 1).

While Petersen et al. do not describe expressing their tissue specific SDF-1 alpha gene expressed via a transactivator comprising a GAL4 DBD, an ODD, and a p65 AD wherein the second nucleic acid

comprises a UAS wherein the transactivator binds the UAS in response to hypoxia, such was taught by Tang2.

Tang2 taught a double vector model comprising a first nucleic acid encoding an oxygen-sensitive transactivator (GAL4/ODD/p65AD) as claimed. The second nucleic acid includes UAS linked to a cardioprotective transgene.

It would have been obvious at the time of filing to the vector control system of Tang2 with the SDF stem cell chemoattractant of Petersen to express exogenous SDF in the heart. One would have been motivate to make such a substitution as Tang2 taught a highly specific control of gene expression in response to hypoxic events using the vector system to express a transgene in the heart only in response to hypoxia. One of ordinary skill in the art would have been afforded a reasonable expectation of success in carrying out the combination as the vector system was already show to be effective and the technology to exchange the transgene of interest was highly developed such that one could readily make the substitution.

Applicant's arguments regarding this rejection were combined with those reiterated and addressed above. The rejection is maintained, therefore, for reasons set forth above.

Claims 17,23 and 44 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Petersen et al. (U.S. Patent Publication No.: 2002/0094327; effective filing date: Nov. 5, 2000), in view in view of Tang et al. (Methods, 28:259-266, 2002; referred to as Tang2), as applied to claims above, and further in view of Kovesdi (USPGPUB 2003/0027751).

The teachings of Petersen and Tang2 are set forth above. Neither reference teaches coadministration of stem cells.

Kovesdi et al. describe vectors that include polynucleotides encoding VEGF fusion proteins that

promote angiogenesis and wound healing (Abstract). Kovesdi et al. disclose that the vector may be administered to any cardiac tissue of the heart (paragraph [0161], and additionally co-administered with factors such as GM-CSF, in association with the administration of stem cells (paragraph [0171], thus curing the deficiency in Petersen et al.

As the disclosure of Petersen et al., and Kovesdi et al. are directed to gene delivery to the heart of a subject and further recruitment of stem cells to the target tissue, it would have been *prima facie* obvious for a person of ordinary skill in the art, to combine their respective teachings and to co-administer stem cells with the vector of Petersen as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would be motivated to co-administer stem cells with a therapeutic polynucleotide to the heart of a subject, because such was specifically taught by Kovesdi et al. and would result in increased wound healing and tissue repair.

Applicant's arguments regarding this rejection were combined with those reiterated and addressed above. The rejection is maintained, therefore, for reasons set forth above.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to VALARIE BERTOGLIO whose telephone number is (571)272-0725. The examiner can normally be reached on Mon-Fri 6:30-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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